

REMARKS

Applicants respectfully request the Examiner to reconsider the present application in view of the foregoing amendments to the claims and the following remarks.

Status of the Claims

Claims 4-9 and 14-23 are pending in this application. Claims 6-9 are withdrawn from consideration. Claim 4 is independent.

In the present Amendment, claims 17-23 have been added. Claims 1-3 were previously canceled without prejudice or disclaimer of the subject matter contained therein.

No new matter has been added with the addition of claims 17-23. Support for these new claims is found throughout the present specification, such as page 6-7 and the examples.

Reconsideration of this application, as amended, is respectfully requested.

Substance of the Interview

Applicants thank the Examiner for her time, helpfulness and courtesies extended to Applicants' representative during the Interview of January 10, 2011. The assistance of the Examiner in advancing prosecution of the present application is greatly appreciated. In compliance with M.P.E.P. § 713.04, Applicants submit the following remarks.

The Interview Summary form amply summarizes the discussions at the Interview. Applicants' Representative argued that the primary reference discloses an intermediate compound, and thus the reference is improperly cited. Applicants' Representative also argued that the cited secondary reference is improperly cited, as this is a general review article showing

specific substitutions for a different class of compounds. The arguments presented during the Interview are repeated below.

Rejection under 35 U.S.C. § 103(a)

Claims 4-5 and 14-16 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over **Fourtillan '471** (U.S. Patent No. 5,763,471) in view of **Patani** (*Chem. Rev.*, Vol. 96, pp. 3146-3176 (1996)). This is a new rejection. Applicants respectfully traverse.

The obviousness inquiry is decided as a matter of law, based on four general factual inquiries as explained in *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966), and reaffirmed in *KSR Int'l, Inc. v. Teleflex, Inc.*, 550 U.S. 398, 406-07 (2007). Here, those *Graham* factors weigh in Applicants' favor, and a proper rationale has not been used to reject the disputed claims. Regarding the *Graham* factors of determining the scope and content of the prior art, ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art, Applicants submit the following.

The actual disclosure, including the intermediate compound, of Fourtillan '471

In the Office Action, the Examiner refers to the compound of formula IIa in Fourtillan '471 (see column 3, lines 49-56) and states what Fourtillan '471 substituents are to correspond to the instantly claimed substituents of the formula (I') recited in pending claim 4. Regarding Fourtillan '471, the Examiner also states, "The compound can be used for the treatment of disorders associated with melatonin disorders in a pharmaceutical and cosmetic compositions (abstract)." The Examiner acknowledges that Fourtillan '471 fails to disclose a compound

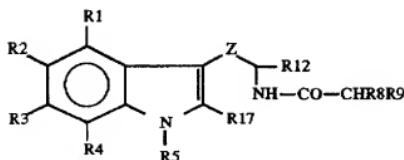
wherein the instantly claimed compound has R³ and R⁵ as being the same or different, and R³ and R⁵ each represents a halogen atom (Office Action, page 4). Thus, Patani is cited to account for such deficiencies of the primary reference.

The basis for citing Patani and combining this reference with Fourtillan '471 is improper. One of ordinary skill in the art would simply not take the Fourtillan '471 compound and make so many substitutions that may lead to the present invention. There is simply no basis for this.

The Examiner explains that Patani gives a basis for modifying a lead compound, such as replacing a hydrogen atom with fluorine (Office Action, page 4, second and third full paragraphs). Applicants respectfully submit that Fourtillan '471 does not provide a "lead compound".

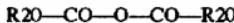
In fact, Fourtillan '471 describes the following at column 3, line 40 to column 4, line 15 (Applicants' emphasis added below):

In the particular case where R11 represents an oxygen atom, R10 represents a perhalo(lower)alkyl (-R20) radical, R5 represents a perhalo(lower)alkylcarbonyl (-CO-R20) radical, R6 represents a hydrogen atom and R7 represents a perhalo(lower)alkylcarbonyloxy (-O-CO-R20) radical, *the derivatives of formula Ia may be obtained directly by reacting the compound of general formula IIa*



IIa

for which R1, R2, R3, R4, R5, R8, R9, R12 and Z are defined above and R17 represents a hydrogen atom, *with an excess of anhydride of formula III*

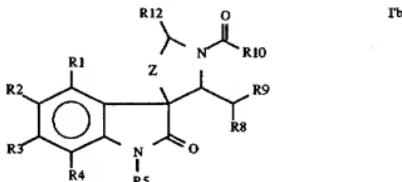


III

in which R20 represents a perhalo(lower)alkyl residue.

The derivatives of general formula I, for which –X=Y– represents a divalent radical of formula Ib, R11 represents an oxygen atom and R10 represents a perhalo(lower)alkyl (–R20) radical, are obtained by reacting a derivative of general formula IIa as defined above, and in which R17 represents a bromine atom, with an excess of anhydride of formula III defined above.

The derivative of general formula I'b



in which R10 represents a perhalo (lower) alkyl radical, is thus obtained.

In this regard, any cited reference used for a rejection under 35 U.S.C. § 103(a) must be considered in its entirety, *i.e.*, as a whole, including those portions that would lead away from a claimed invention. *See W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). Here, the invention of Fourtillan '471 is the derivatives of formula I, Ia or Ib. The compounds of formula IIa are merely intermediate compounds for producing the derivatives of general formula Ia and/or Ib. Thus, based on an entire reading of Fourtillan '471, one of ordinary skill in the art would not achieve the present invention, nor would the skill artisan have a proper rationale in achieving the present invention.

KSR Int'l, supra.

Applicants also note MPEP 2144.09(VI), ("IF PRIOR ART COMPOUNDS HAVE NO UTILITY, OR UTILITY ONLY AS INTERMEDIATES, CLAIMED STRUCTURALLY SIMILAR COMPOUNDS MAY NOT BE *PRIMA FACIE* OBVIOUS OVER THE PRIOR

ART", which states, "If the prior art does not teach any specific or significant utility for the disclosed compounds, then the prior art is **>unlikely< to render structurally similar claims *prima facie* obvious **>in the absence of any reason< for one of ordinary skill in the art to make the reference compounds **>or< any structurally related compounds." (Citing *In re Stemniski*, 444 F.2d 581, 170 USPQ 343 (CCPA 1971).)

Hindsight reconstruction; no reasonable expectation of success

There is no basis in the cited Patani reference to modify the intermediate of Fourtillan '471. The application of hindsight is inappropriate where the prior art does not suggest that the claimed compound/composition could reasonably be expected to manifest the properties and advantages that were found for the claimed invention. *Sanofi-Synthelabo v. Apotex, Inc.*, 89 USPQ2d 1370, 1379 (Fed. Cir. 2008) (citing *Graham v. John Deere Co.*, 383 U.S 1, 36 (cautioning against hindsight whereby the teachings of the invention are read into the prior art) and *KSR Int'l Co. v Teleflex Inc.*, 82 USPQ2d 1385, 1397 (recognizing "hindsight bias" and "ex post reasoning" as inappropriate in determination of obviousness)). Here, the cited compound of Fourtillan '471 is an intermediate, and the properties thereof cannot possible be expected to manifest properties of activating osteoclasts and suppressing osteoclasts. Instead, the present rejection is based on *ex post*, improper hindsight reasoning.

Furthermore, the actual compounds in Patani are, e.g., napthyl-fused diazepines (see right column of page 3149), which are not the same as the instantly claimed class of compounds. If the Examiner is applying the generic disclosure of Patani to the instantly claimed specific class of compounds, Applicants traverse and believe there is no scientific basis to do so. Patani is a

general review article that does not automatically apply to the instant art. Also, Applicants note M.P.E.P. § 2143.02, which states that the prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. *In re Merck & Co., Inc.*, 231 USPQ 375 (Fed. Cir. 1986). However, in finding a reasonable expectation of success, at least some degree of predictability is required. *In re Rinehart*, 189 USPQ 143 (CCPA 1976). Such a level of predictability is absent here, especially given how the Patani reference describes different class of compounds with different possible substitutions. If anything, there is undue experimentation involved, wherein the Patani reference would not be enabling. In this regard, a cited modification/combination of a reference(s) must be enabling such that one of ordinary skill in the art can make the claimed invention (e.g., the claimed invention is in the possession of the public). *In re Brown*, 51 CCPA 1254, 1259, 141 USPQ 245, 249 (CCPA 1964); *see also In re Payne*, 606 F.2d 303, 314, 203 USPQ 245, 255 (CCPA 1979).

Regarding the fourth *Graham* factor, Applicants point out that the instantly claimed compounds function to activate osteoclasts and suppress osteoclasts. Such compounds are useful for pharmaceutical compositions to treat various bone-related diseases, such as a pharmaceutical composition for preventing or treating osteoporosis, or as an osteoblast activator and an osteoclast suppressor, in various fields, such as regenerative medicine, dentistry, or production of edible meats or eggs via fish cultivation or healthy development of livestock (see page 9, line 24 to page 10, line 2, and Example 15 of the present specification). Neither Fourtillan '471 nor Patani teaches or suggests the above effects of the instantly claimed compounds. Fourtillan '471 merely discloses an intermediate compound.

“Lead compound” analysis; Patani improperly combined with Fourtillan ‘471

Also, though the Examiner cites the Patani reference asserting that the skilled artisan would make the modification of, e.g., replacing hydrogen with fluorine, Applicants note the following U.S. case law surrounding the “lead compound” analysis.

While the courts have adopted a more flexible teaching/suggestion/motivation (TSM) test in connection with the obviousness standard based on the *KSR v. Teleflex* case which involved a mechanical device in a relatively predictable technological area, it remains true that, despite this altered standard, the courts recognize inventors face additional barriers in relatively unpredictable technological areas. For instance, in *Takeda Chem. Industries, Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1358, 1362-63 (Fed. Cir. 2007) and *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008), a *prima facie* case of obviousness depended on whether the prior art provided a suggestion or reason to choose a specific lead compound for modification, or to make the specific modification of the compound at issue.

Applicants also note *Eisai Co. Ltd. v. Dr. Reddy's Laboratories Ltd.*, 87 USPQ2d 1452 (Fed. Cir. 2008), wherein it was determined that a *prima facie* case of obviousness for a chemical compound generally begins with identification of “lead” compound that is modified to achieve the claimed compound. In *Eisai*, the plaintiffs were properly granted summary judgment that it would not have been obvious to modify the lead compound (lansoprazole) to obtain the claimed compound (rabeprazole) having anti-ulcerative activity since the important substituent of the prior art chemical compound (lansoprazole having fluorinated substituent) would have to be removed to attain the claimed invention (rabeprazole with a different substituent).

Similarly, in *Sanofi-Synthelabo v. Apotex Inc.*, 89 USPQ2d 1370 (Fed. Cir. 2008), the

Federal Circuit affirmed the lower court decision holding that a claim for clopidogrel compositions used in blood platelet aggregation inhibition, which recites bisulfate salt of a dextrorotatory enantiomer of a specific compound substantially separated from its levorotatory enantiomer, is not invalid for obviousness over prior art references that disclose the racemate from which the dextrorotatory enantiomer may be separated. In *Sanofi-Synthelabo*, the court found that a person of ordinary skill in art would not reasonably have predicted from the reference's disclosure that the dextrorotatory enantiomer would provide desired antiplatelet activity without adverse neurotoxicity, that separation of enantiomers was not simple or routine procedure, and that success in separation, as well as allocation of properties, was unpredictable, and since patent in suit claims bisulfate salt, whereas PCR 4099 racemate is hydrochloride, and both parties' experts agreed that whether pharmaceutically suitable crystalline salt will form from particular acid-base combination is unpredictable. Thus, there was no "combination of familiar elements according to known methods" that "does no more than yield predictable results."

An issue in the mentioned U.S. case law was whether the prior art provided a suggestion or reason to choose a specific lead compound for modification, and/or whether to make the specific modification of the compound at issue. In the instant situation, a "lead compound" is not even identified. Again, Fourtillan '471 merely discloses formula IIa as an intermediate in making the final compound of formula Ia (see column 3, lines 40-60), and not an isolated compound. The compound of formula IIa is, e.g., reacted with the "excess of anhydride of formula III" to make the compound of formula Ia (see column 3, lines 45-46 and 56-60). An intermediate as described in Fourtillan '471 is not a "lead" compound. Nor does Patani make such an identification to modifying an intermediate compound. Thus, there is no proper *KSR*

Int'l rationale in combining Fourtillan '471 with Patani.

Summary

Accordingly, for the reasons stated herein, claims 4, 5 and 14-16 are patentable over Fourtillan '471 in view of Patani. The *Graham* factors weigh in Applicants' favor, and the rationale in combining the cited references is improper. Thus, reconsideration and withdrawal of this rejection are respectfully requested.

Request for Rejoinder and New Claims

Applicants also submit that claim 4, and any claim dependent thereon, is in allowable condition. Thus, Applicants respectfully submit that composition and method claims 6-9 should be rejoined and found allowable as well pursuant to *In re Ochiai*, 37 USPQ2d 1127 (Fed. Cir. 1995).

Newly added claims 17-23 correspond to the elected subject matter. Applicants also request allowance of newly added claims 17-23. These claims depend on claim 4, and thus are allowable for the same reasons given herein.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. It is believed that a full and

Reply to Office Action of November 12, 2010

complete response has been made to the outstanding Office Action, and as such, the present application is in condition for allowance.

In view of the above amendment, Applicant believes the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Eugene T. Perez, Registration No. 48,501, at the telephone number of the undersigned below to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Director is hereby authorized in this, concurrent, and future replies to charge any fees required during the pendency of the above-identified application or credit any overpayment to Deposit Account No. 02-2448.

Dated: JAN 26 2011

Respectfully submitted,

By Gerald M. Murphy, Jr.
Gerald M. Murphy, Jr.
Registration No.: 28977
BIRCH, STEWART, KOLASCH & BIRCH, LLP
8110 Gatehouse Road, Suite 100 East
P.O. Box 747
Falls Church, VA 22040-0747
703-205-8000